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(54) Title: PROCESS FOR THE PREPARATION OF AZAMACROCYLCIC OR ACYCLIC AMINOPHOSPHONATE ESTER DERIVATIVES

(57) Abstract

A novel process for the preparation of azamacrocyclic or acyclic aminophosphonate ester derivatives is disclosed. The process concerns the reaction of an appropriate azamacrocyclic or acyclic primary or secondary amine with trialkyl phosphite and paraformaldehyde.

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PROCESS FOR THE PREPARATION OF AZAMACROCYCLIC OR ACYCLIC AMINOPHOSPHONATE ESTER DERIVATIVES

This invention concerns a novel process for the preparation of azamacrocyclic or acyclic aminophosphonate ester derivatives. Such process provides ligands which are useful as diagnostic or therapeutic agents.

Macrocyclic aminophosphate esters are receiving considerable attention as diagnostic and therapeutic agents. The general synthetic methodology for preparing chelating agents of this type utilizes an amine in combination with phosphorous acid, formaldehyde and hydrochloric acid to provide the aminophosphonic acid, e.g. 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylenephosphonic acid (DOTMP). Alternatively, methylenephosphonate functionality can be introduced by substituting a di- or tri-alkyl phosphite in the place of phosphorous acid in the prior procedure, to generate the corresponding dialkylphosphonate ester. These esters can be hydrolyzed under basic conditions to give the monoalkyl-phosphonate half esters. In addition, these full esters can be hydrolyzed under acidic conditions to give phosphonic acids, e.g. DOTMP (see published application WO 91/07911). The general synthetic approach to aminophosphonates using either di- or tri-alkyl phosphites is documented in the literature by the reaction of various linear amines and using standardized procedures.

The present invention is directed to a process for preparing azamacrocyclic or acyclic aminophosphonate ester derivatives which possess at least one secondary or primary nitrogen atom substituted with at least one moiety of the formula

$$-CH_2PO_3RR^1 \quad (I)$$

wherein:

R is H or C_1-C_5 alkyl; with the proviso that each R is the same group;

R^1 is C_1-C_5 alkyl, H, Na or K; with the proviso that each R and R^1 is the same group when C_1-C_5 alkyl;

which comprises reacting the corresponding unsubstituted amine compound with a trialkyl phosphite and paraformaldehyde to provide the derivatives of Formula (I) wherein all R and R^1 equal C_1-C_5 alkyl; and

(a) optionally followed by aqueous base hydrolysis to provide the derivatives of Formula (I) wherein R is C_1-C_5 alkyl and R^1 is H, Na or K; and/or

(b) optionally followed by acid hydrolysis to provide the derivatives of Formula (I) wherein all R and R^1 equal H.

When the above ligands of Formula (I) have:

(i) all R and R^1 equal H, the ligands are referred to as phosphonic acids;

(ii) all R equal H, and all R^1 equal C_1-C_5 alkyl, the ligands are referred to herein as phosphonate half esters; and

(iii) all R and R^1 equal C_1-C_5 alkyl, th ligands are r ferred to as phosphonate esters.

In some of our copending applications and patents we have discussed the use of these azamacrocyclic or acyclic aminophosphonate ester derivatives of Formula (I) as diagnostic agents. Particularly, the half esters are useful as tissue specific magnetic resonance imaging (MRI) contrast agents when chelated with gadolinium. Several azamacrocyclic or acyclic aminophosphonic acids, e.g. DOTMP or EDTMP, when chelated with samarium-153 are useful as pain relief agents for calcific tumors in cancer patients.

The compounds of Formula (I) which are azamacrocyclic or acyclic aminophosphonate ester derivatives which possess at least one secondary or primary nitrogen atom substituted with at least one moiety of the formula

$$-CH_2PO_3RR^1 \quad (I)$$

wherein:

R is H or C_1-C_5 alkyl; with the proviso that each R is the same group;

R^1 is C_1-C_5 alkyl, H, Na or K; with the proviso that each R and R^1 is the same group when C_1-C_5 alkyl;

encompass known ligands and also those claimed in our copending applications.

The ligands used as starting materials to make the compounds of Formula (I) are known in the art. Some examples of these acyclic amine ligands are

ethylenediamine (EDA);

diethylenetriamine (DTA);

triethylenetetraamine (TTA); and

numerous known linear or branch chain primary or secondary amines.

Some examples of azamacrocyclic amine ligands are

1,4,7,10-tetraazacyclododecane (Cyclen); and

other known secondary azamacrocyclic amines.

The azamacrocyclic or acyclic aminophosphonate derivatives encompassed with a moiety of Formula (I) must have at least one secondary or primary nitrogen which is substituted with the moiety of Formula (I). Preferably, the number of nitrogen atoms present which may be substituted by a moiety of Formula (I) is from 2 to 10, preferably from 2 to 6. Usually the nitrogen atoms are separated from each other by at least two carbon atoms. Thus these derivatives can be represented by the formula

$$A\text{-}(N\text{-}CH_2CH_2\text{-}N)q\text{-}Z \quad (II)$$

wherein:

q is an integer from 1 to 5 inclusive;

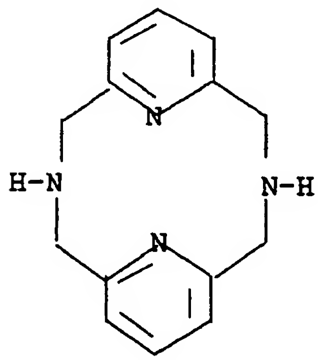
A may be 0, 1 or 2 moieti s of F rmula (I) or hydrogen;

Z may be 0, 1 or 2 moieti s of Formula (I) or hydrogen;

with the proviso that at least one A or Z moiety of Formula (I) is present; and

A and Z may be joined to form a cyclic compound.

Examples of suitable azamacrocyclic amine ligands that are discussed in our copending applications are shown by the following formula: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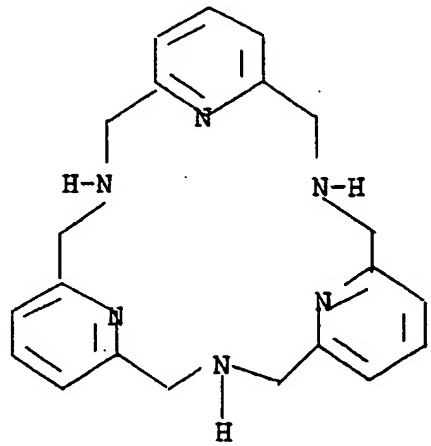
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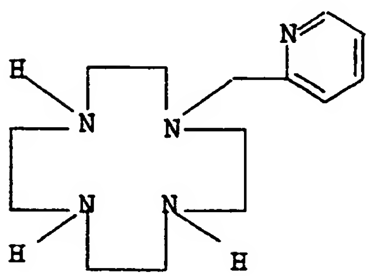
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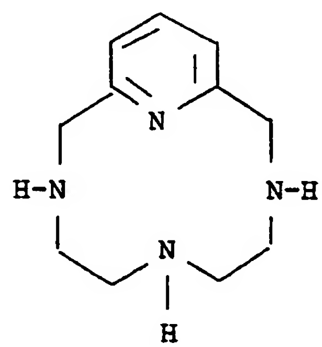
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The terms used in Formula (I) and for this invention are further defined as follows. "C_1-C_5 alkyl", include both straight and branched chain alkyl groups. "Trialkyl phosphite" includes any alkyl which in the resulting product of Formula (I) has desirable water solubility following hydrolysis, e.g. tri(C_1-C_{10} alkyl) phosphite, preferably tri(C_1-C_4 alkyl) phosphite, including both straight and branched chain alkyl groups.

When the azamacrocyclic ligands of Formula (I) wherein the full esters (R and R^1 are both the same C_1-C_5 alkyl) are prepared, pressure is not critical so that ambient pressure is used. As the reaction is exothermic, the temperature is controlled to be maintained below 40°C during the first hour; and after the first hour, the temperature can be raised to facilitate completion of the reaction but need not exceed about 90°C. The pH of the reaction is not critical and the reaction is non-aqueous. The reaction is run in the presence of a non-aqueous liquid, such as the trialkyl phosphite reagent or a solvent. A solvent is preferably used; examples of such solvents are: aprotic polar solvents such as tetrahyrdofuran (THF), dioxane, acetonitrile, and other similar inert, non-aqueous solvents; alcohols where the alkyl portion is the same as the R obtained, such as methanol, ethanol and propanol. THF is the preferred

solvent. The order of addition of the reactants and the azamacrocyclic or acyclic aminophosphonate starting material is not critical.

When the acyclic ligands of Formula (I) wherein th full esters (R and R^1 are both the same C_1-C_5 alkyl) are prepared, the reaction is significantly more exothermic. It is critical to control the temperature below 40°C for the first hour of the reaction. Methods to effectively control the temperature are known, such as the presence of an ice bath, dilution with solvents or the order and/or speed of addition of reagents. For example, one method involves combining the trialkyl phosphite and paraformaldehyde and initially cooling the mixture, followed by the controlled addition of the acyclic amine, while maintaining the temperature by using an ice bath.

All the ligands of Formula (I) wherein the half esters are prepared (R = C_1-C_5 alkyl and R^1 = H, Na or K) by aqueous base hydrolysis is accomplished after the formation of the corresponding full ester. Examples of suitable bases are alkali metal hydroxides, e.g. sodium or potassium hydroxide. The amount of base used is from about 1-10 equivalents per secondary amine or 2-20 equivalents per primary amine. As the alkyl chain length of the R or R^1 group is propyl or higher, then a cosolvent is used with the water. Suitable examples of such cosolvents are organic water miscible solvent, such as 1,4-dioxane, THF and acetone.

The full acids of the ligands of Formula (I) may be made from the corresponding half esters or full esters under known acidic hydrolysis conditions (see published application WO 91/07911).

The present process is advantageous over those methods known in the art for the following reasons. The prior processes in which dialkyl phosphites under aqueous conditions are used give good results for acyclic amines, but less predictable results are obtained when macrocyclic ligands are employed. Furthermore, the macrocyclic ligand cyclen is used, none of the desired ester is isolated. In contrast to the art, when the present process is used, the desired products of Formula (I) are obtained in all instances with yields in excess of 90%.

The invention will be further clarified by a consideration of the following examples, which are intended to be purely exemplary of the present invention. Some terms used in the following examples are defined as follows: g = gram(s); mg = milligrams; kg = kilogram(s); mL = milliliter(s); µL = microliter(s).

General Materials and Methods.

All reagents were obtained from commercial suppliers and used as received without further purification. NMR spectra were recorded on a Bruker AC-250 MHz spectrometer equipped with a multi-nuclear quad probe (^1H, ^{13}C, ^{31}P, and ^{19}F) at 297°K unless otherwise indicated. ^1H spectra in D_2O were recorded by employing solvent suppression pulse sequence ("PRESAT", homo-nuclear presaturation). ^1H spectra are referenced to residual chloroform (in $CDCl_3$) at δ7.26 or external dioxane (in D_2O) at δ3.55. ^{13}C and ^{31}P spectra reported are proton decoupled (broad band). Assignments of ^{13}C {^1H} chemical shifts were aided by DEPT (Distortionless Enhancement by Polarization Transfer) experiments. ^{13}C {^1H} spectra are referenced to center peak of $CDCl_3$ at δ77.00 (in $CDCl_3$) and external dioxane at δ66.66 (in D_2O). ^{31}P {^1H} spectra were referenced to external 85% H_3PO_4 at δ0.00. Melting points were determined by capillary melt methods and were uncorrected. Semipreparative ion-exchange chromatographic separations were performed at low pressure (<600 psi) using a standard glass column fitted with hand-packed Q-Sepharose™ (anion exchange) or SP--Sepharose™ (cation exchange) glass column, and with on-line UV detector at 263 nm for eluent monitoring. GC/MS spectra were performed on a Hewlett Packard 5890A Gas Chromatograph/ 5970 Mass Selective Detector.

The process to make the full ester derivatives of Formula (I) has been discussed before. A typical procedure is as follows:

Example 1: Process for preparing 1,4,7,10-tetraazacyclododecane-1,4,7,10-methylenedibutyl phosphonate.

Cyclen, 10 g (58 mmol), tributyl phosphite, 62 g (246 mmol) and paraformaldehyde, 7.4 g (246 mmol) were combined in 70 mL of THF and stirred at room temperature (the temperature was maintained below 40°C) for 24 hrs. The homogeneous solution was then concentrated *in vacuo* to give a viscous oil (quantative yield) and characterized by:

^1H NMR ($CDCl_3$)

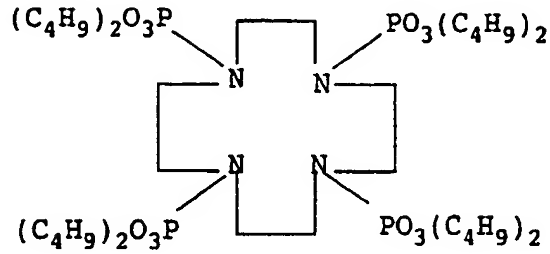
δ 0.88 (m, 24H), 1.33 (m, 16H), 1.59 (m, 16H), 2.80 (s, 16H), 2.90 (d, 8H), 4.00 (m, 16H); and

^{13}C {^1H} NMR ($CDCl_3$)

δ 13.51, 18.65, 32.49, 32.57, 49.04, 51.45, 53.10, 53.18; and

^{31}P NMR ($CDCl_3$)

δ 26.16 (s, 4P); and is illustrated by the formula



Example 2: Process for preparing 1,4,7,10-tetraazacyclododecane-1,4,7,10-methylenediethyl phosphonate.

When the procedure of Example 1 was repeated using triethyl phosphite in place of the tributyl phosphite, the title compound was obtained as viscous oil in greater than 98% yield and characterized by:

^{1}H NMR ($CDCl_3$)

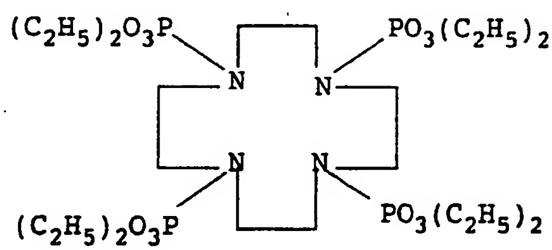
δ 1.19 (m, 24H), 2.71 (s, 16H), 2.80 (d, 8H), 4.01 (m, 16H); and

$^{13}C\{^{1}H\}$ NMR ($CDCl_3$)

δ 15.32, 15.42, 42.23, 51.67, 53.18, 53.28, 61.34, 61.45; and

^{31}P NMR ($CDCl_3$)

δ 26.02 (s, 4P); and is illustrated by the formula



Example 3: Preparation of N,N'-bis(methylenedimethylphosphonate)-2,11-diaza[3.3](2,6)pydinophane.

When the procedure of Example 1 was repeated using trimethyl phosphite in place of the tributyl phosphite and 2,11-diaza[3.3](2,6)pydinophane in place of Cyclen, the title compound was obtained as a very viscous oil in greater than 95% yield and further charact rized by:

^{1}H NMR ($CDCl_3$)

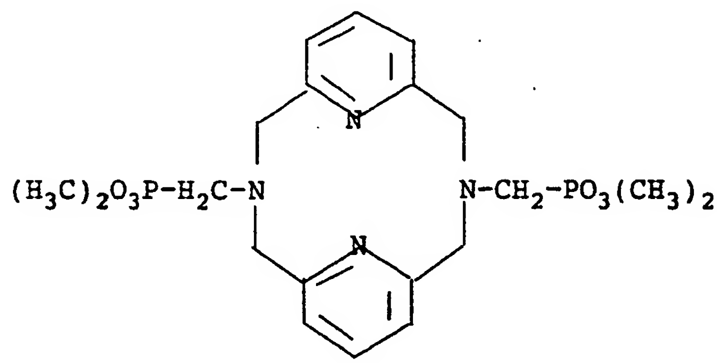
δ 3.39 (d, 4H), 3.88 (d, 12H), 4.08 (s, 8H), 6.84 (d, 4H), 7.13 (t, 2H); and

^{13}C {^{1}H} NMR ($CDCl_3$)

δ 52.75 (d), 54.88 (d), 65.21 (d), 122.71, 135.69, 157.14; and

^{31}P NMR ($CDCl_3$)

δ 27.22; and is illustrated by the formula



Example 4: Preparation of N,N'-bis(methylenediethylphosphonate)-2,11-diaza[3.3](2,6)pydinophane.

When the procedure of Example 1 was repeated using triethyl phosphite in place of the tributyl phosphite and 2,11-diaza[3.3](2,6)pydinophane in place of Cyclen, the title compound was obtained as a very viscous oil in greater than 95% yield and further characterized by:

^{1}H NMR ($CDCl_3$)

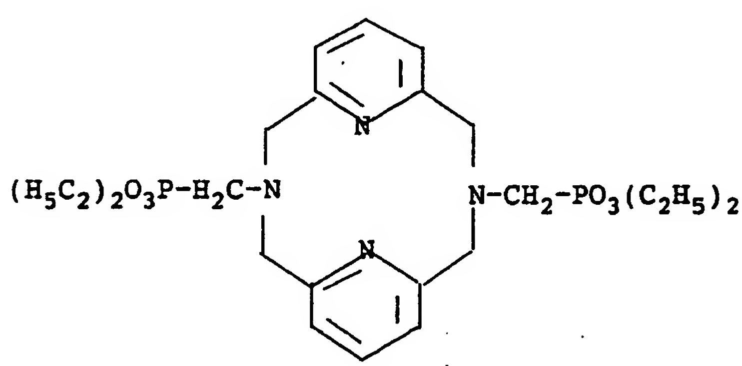
δ 1.24 (t, 12H), 3.20 (d, 4H), 3.94 (s, 8H), 4.07 (q, 8H), 6.71 (d, 4H), 6.98 (t, 2H); and

^{13}C {^{1}H} NMR ($CDCl_3$)

δ 16.48, 55.36 (d), 61.75 (d), 65.14 (d), 122.52, 135.41, 157.04; and

^{31}P {^{1}H} NMR ($CDCl_3$)

δ 24.60; and is illustrated by the formula



Example 5: Preparation of N-(2-pyridylmethyl)-N',N'',N'''-tris(methyl nedi thylphosphonate)-1,4,7,10-tetraazacyclododecane.

When the procedure of Example 1 was repeated using triethyl phosphite in place of the tributyl phosphite and N-(2-pyridylmethyl)-1,4,7,10-tetraazacyclododecane in place of Cyclen, the title compound was obtained as a very viscous oil in greater than 95% yield and further characterized by:

^{1}H NMR ($CDCl_3$)

δ 1.25 - 1.39 (m, 18H), 2.66 - 2.95 (m, 22H), 3.71 (s, 2H), 4.01 - 4.22 (m, 12H), 7.10 - 7.15 (m, 1H), 7.57 - 7.65 (m, 2H), 8.46 - 8.52 (m, 1H);

$^{13}C\{^{1}H\}$ NMR ($CDCl_3$)

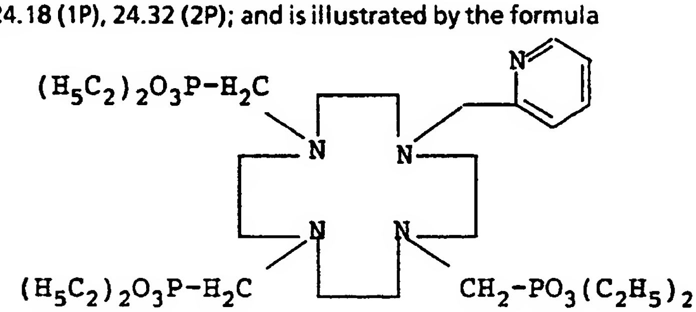
δ 16.38, 16.46, 50.45, 50.67, 52.41, 53.19, 53.29, 53.48, 53.58, 61.37, 61.47, 61.52, 121.67, 123.28, 136.19, 148.61, 159.90; and

$^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 297°K)

δ 26.21;

$^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 217°K)

δ 24.18 (1P), 24.32 (2P); and is illustrated by the formula



Example 6: Preparation of N-(2-pyridylmethyl)-N',N'',N'''-tris(methylenedipropylphosphonate)-1,4,7,10-tetraazacyclododecane.

When the procedure of Example 1 was repeated using tripropyl phosphite in place of the tributyl phosphite and N-(2-pyridylmethyl)-1,4,7,10-tetraazacyclododecane in place of Cyclen, the title compound was obtained as a viscous oil in greater than 95% yield and further characterized by:

^{1}H NMR ($CDCl_3$)

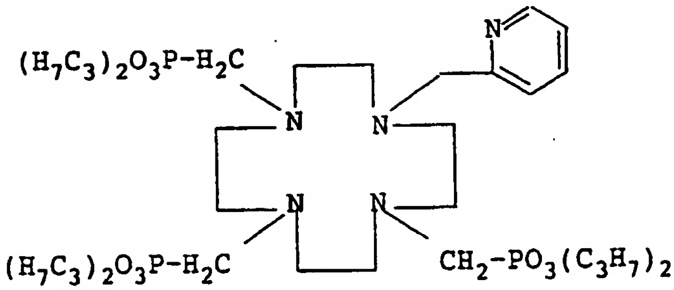
δ 0.91 - 1.00 (m, 18H), 1.60 - 1.76 (m, 12H), 2.67 - 2.99 (m, 22H), 3.73 (s, 2H), 3.94 - 4.08 (m, 12H), 7.12 - 7.15 (m, 1H), 7.46 - 7.67 (m, 2H), 8.48 - 8.52 (m, 1H);

$^{13}C\{^{1}H\}$ NMR ($CDCl_3$)

δ 9.93, 10.21, 23.71, 23.80, 50.17, 50.44, 52.38, 53.09, 53.44, 61.44, 66.79, 66.83, 121.61, 123.23, 136.14, 148.54, 159.92; and

$^{31}P\{^{1}H\}$ NMR ($CDCl_3$)

δ 26.20 (1P), 26.23 (2P); and is illustrated by the formula



Example 7: Preparation of 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-methylenediethylphosphonate.

When the procedure of Example 1 was repeated using triethyl phosphite in place of the tributyl phosphite and 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene in place of Cyclen, the title compound was obtained as a viscous oil in greater than 95% yield and further characterized by:

^1H NMR ($CDCl_3$)

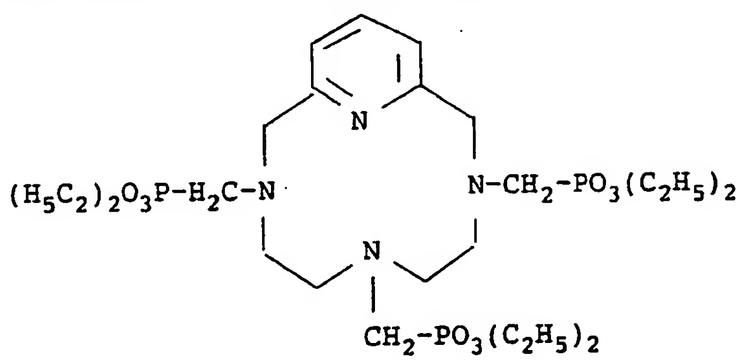
δ 1.23 (m, 18H), 2.77 (m, 12H), 3.04 (d, 6H), 4.13 (m, 12H), 7.17 (d, 2H), 7.60 (t, 1H); and

^{13}C NMR ($CDCl_3$)

δ 16.43, 50.03, 50.31, 50.43, 50.77, 51.23, 51.38, 52.63, 53.30, 60.86, 60.92, 61.63, 61.74, 61.83, 61.93, 62.32, 76.46, 76.97, 77.18, 77.48, 122.50, 137.10, 157.18; and

^{31}P NMR ($CDCl_3$)

δ 24.92 (s, 2P), 24.97 (s,1P); and is illustrated by the formula



Example 8: Preparation of 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1 (15),11,13-triene-3,6,9-methylenedi(n-propyl)phosphonate.

When the procedure of Example 1 was repeated using tripropyl phosphite in place of the tributyl phosphite and 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene in place of Cyclen, the title compound was obtained as a viscous oil in greater than 95% yield and further characterized by:

^1H NMR ($CDCl_3$)

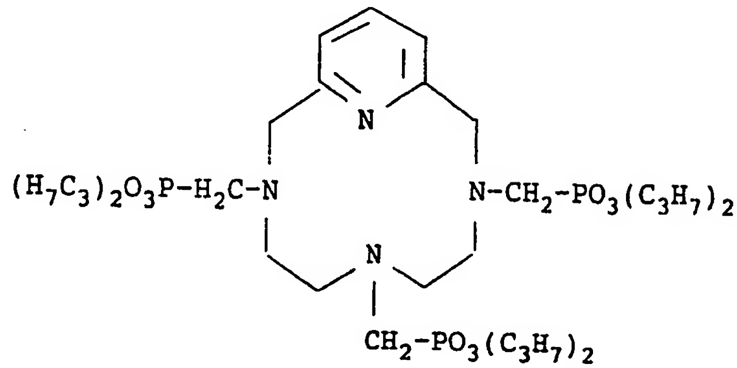
δ 0.88 (m, 18H), 1.61 (m, 12H), 2.72 (m, 12H), 3.03 (d, 6H), 3.97 (m, 12H), 7.13 (d, 2H), 7.55 (t, 1H); and

^{13}C NMR ($CDCl_3$)

δ 9.96, 23.73, 49.84, 50.14, 50.26, 50.57, 51.11, 51.23, 52.43, 53.01, 60.78, 60.84, 67.27, 67.40, 122.48, 137.04, 157.16; and

^{31}P NMR ($CDCl_3$)

δ 24.98 (3P); and is illustrated by the formula



Example 9: Preparation of 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-methylenedi(n-butyl)phosphonate.

When the procedure of Example 1 was repeated using tributyl phosphite in place of the tributyl phosphite and 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene in place of Cyclen, the title compound was obtained as a viscous oil in greater than 95% yield and further characterized by:

^{1}H NMR ($CDCl_3$)

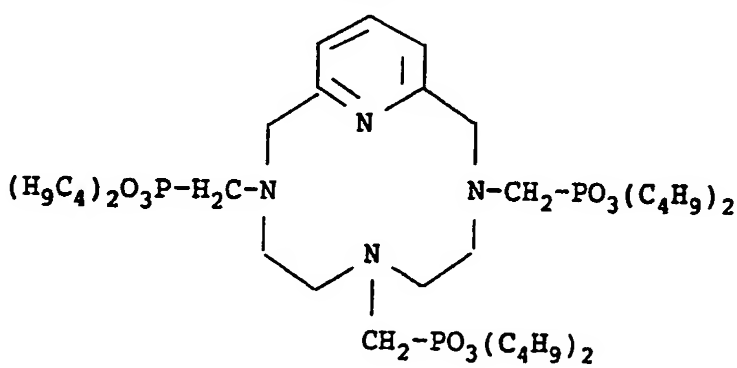
δ 0.84 (m, 18H), 1.27 (m, 12H), 1.58 (m, 12H), 2.57 (m, 12H), 3.01 (d, 6H), 3.99 (m, 12H), 7.12 (d, 2H), 7.54 (t, 1H); and

^{13}C NMR ($CDCl_3$)

δ 13.42, 13.46, 18.50, 18.59, 32.16, 32.43, 49.88, 50.03, 50.16, 50.63, 51.11, 51.27, 52.48, 53.16, 60.71, 60.78, 65.38, 65.48, 65.58, 122.46, 136.96, 157.14; and

^{31}P NMR ($CDCl_3$)

δ 24.88 (2P), 24.93 (1 P); and is illustrated by the formula



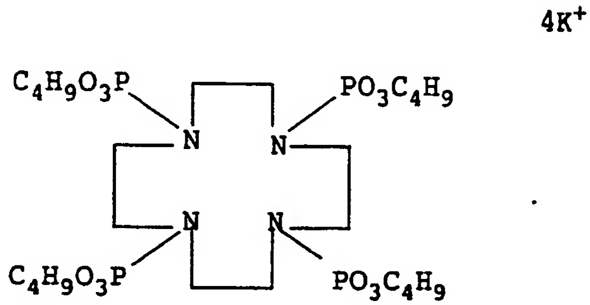
The process to hydrolyze with base the full ester derivatives of Formula (I) to prepare the half esters of Formula (I) has been discussed before. A typical procedure is as follows:

Example 10: Preparation of 1,4,7,10-tetracyclododecane-1,4,7,10-tetramethylenebutylphosphonate, potassium salt.

The ester prepared in Example 1, 3 g (3 mmol) was combined in an aqueous dioxane solution (100 mL water:25 mL dioxane), along with 3 g of KOH (48 mmol). The solution was stirred at reflux for 16 hrs. The one desired titled product was obtained as a solid (94% yield) as characterized by:

^{31}P NMR (D_2O)

δ 21.87 (s, 4P); and is illustrated by the formula



For other ester derivatives where the alkyl ester is C_1-C_3 alkyl, hydrolysis proceeds without the dioxane cosolvent.

Example 11: Preparation of N,N'-bis(methylenephosphonic acid ethyl ester)-2,11-diaza[3.3](2,6)pydinophane (BP2EP).

When the procedure of Example 10 was repeated using ester of Example 4, the title compound was obtained as a solid in greater than 95% yield and further characterized by:

^{1}H NMR (D_2O)

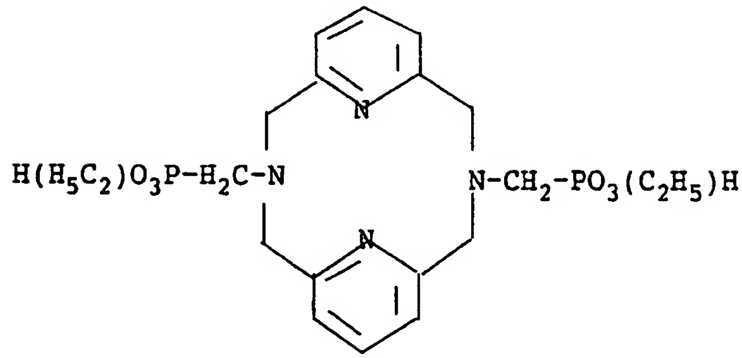
δ 1.10 (t, 6H), 2.97 (d, 4H), 3.81 (q, 4H), 3.84 (s, 8H), 6.73 (d, 4H), 7.09 (t, 2H); and

$^{13}C\{^{1}H\}$ NMR (D_2O)

δ 18.98, 58.76 (d), 63.69 (d), 66.53 (d), 126.35, 140.09, 159.37; and

$^{31}P\{^{1}H\}$ NMR (D_2O)

δ 20.65;; and is illustrated by the formula



Example 12: Preparation of 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-methylene(n-butyl)phosphonate tris(potassium salt) (PMBHE).

When the procedure of Example 10 was repeated using ester of Example 9, the title compound was obtained as a solid in greater than 95% yield and further characterized by:

^{1}H NMR (D_2O)

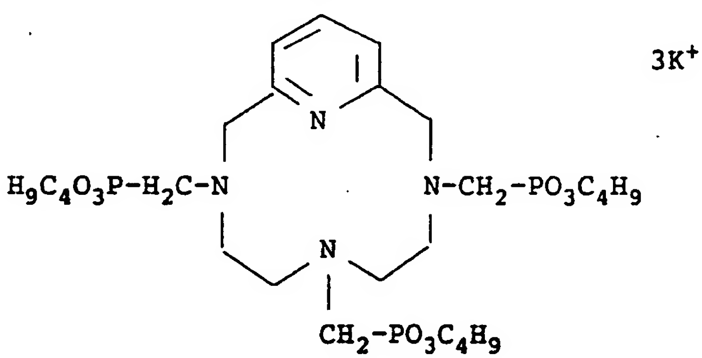
δ 0.68 (m, 9H), 1.14 (m, 6H), 1.37 (m, 6H), 2.76 (d, 6H), 3.41 (m, 12H), 3.73 (m, 6H), 7.24 (d, 2H), 7.76 (t, 1H); and

^{13}C NMR (D_2O)

δ 15.76, 15.80, 21.12, 21.20, 34.96, 35.06, 35.14, 52.08, 52.53, 53.38, 53.48, 54.49, 54.75, 57.70, 57.76, 61.86, 67.65, 67.75, 67.98, 68.08, 125.15, 142.93, 152.25; and

^{31}P NMR

δ 9.73 (s, 2P), 21.00 (s, 1P); and is illustrated by the formula

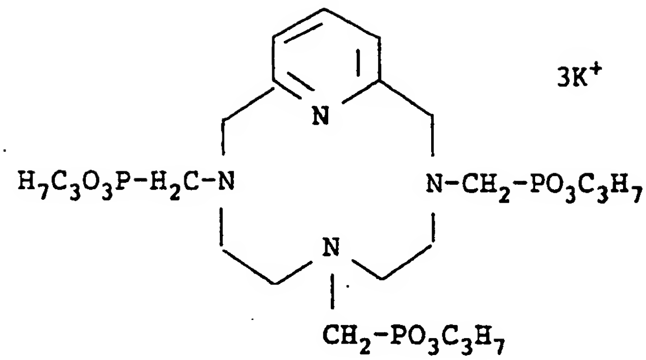


Example 13: Preparation of 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-methylene(n-propyl)phosphonate tris(potassium salt) (PMPHE).

When the procedure of Example 10 was repeated using ester of Example 8, the title compound was obtained as a solid in greater than 95% yield and further characterized by:

^{31}P NMR

δ 20.49 (s, 3P); and is illustrated by the formula



Example 14: Preparation of 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-methyleneethylphosphonate tris(potassium salt) (PMEHE).

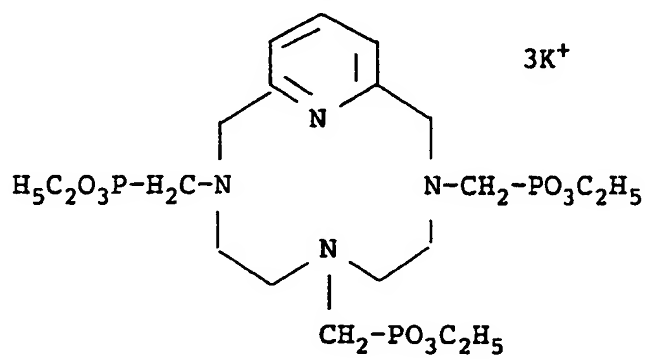
When the procedure of Example 10 was repeated using ester of Example 7, the title compound was obtained as a solid in greater than 95% yield and further characterized by:

^{13}C NMR (D_2O)

δ 18.98, 19.82, 51.78, 52.06, 53.08, 54.46, 54.68, 57.01, 58.22, 60.24, 63.19, 63.25, 63.36, 63.49, 63.59, 63.95, 64.18, 64.25, 66.80, 126.62, 141.63, 159.40; and

^{31}P NMR (D_2O)

δ 20.58 (s, 2P), 20.78 (s, 1P); and is illustrated by the formula



Example 15: Preparation of N-(2-pyridylmethyl)-N',N'',N'''-tris(methylenephosphonic acid ethyl ester)-1,4,7,10-tetraazacyclododecane (PD3EP).

When the procedure of Example 10 was repeated using ester of Example 5, the title compound was obtained as a solid in greater than 95% yield and further characterized by:

^{1}H NMR (D_2O, 338° K)

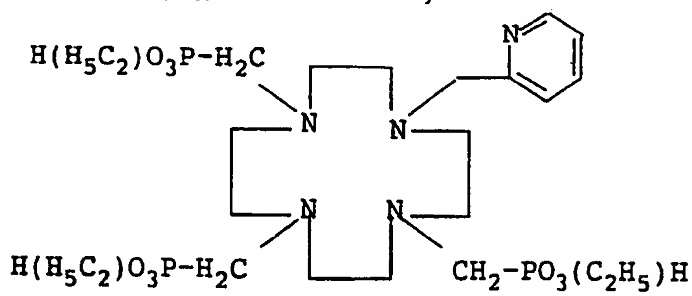
δ 1.41 - 1.57 (m, 9H), 3.28 - 3.89 (m, 22H), 4.09 - 4.64 (m, 8H), 8.22 - 8.26 (m, 2H), 8.70 - 8.75 (m, 1H), 9.00 - 9.12 (m, 1H); and

$^{13}C\{^{1}H\}$ NMR (D_2O, 338° K)

δ 19.41, 19.51, 52.58, 53.00, 52.31, 53.75, 53.82, 56.04, 59.53, 64.60, 64.76, 129.86, 131.41, 147.31, 149.06, 154.34; and

$^{31}P\{^1H\}$ NMR (D_2O, 338°K)

δ 9.64 (2P), 19.79 (1P); and is illustrated by the formula



Example 16: Preparation of N-(2-pyridylmethyl)-N',N'',N'''-tris(methylenephosphonic acid propyl ester)-1,4,7,10-tetraazacyclododecane (PD3PP).

When the procedure of Example 10 was repeated using ester of Example 6, the title compound was obtained as a solid in greater than 95% yield and further characterized by:

^1H NMR (D_2O, 353° K)

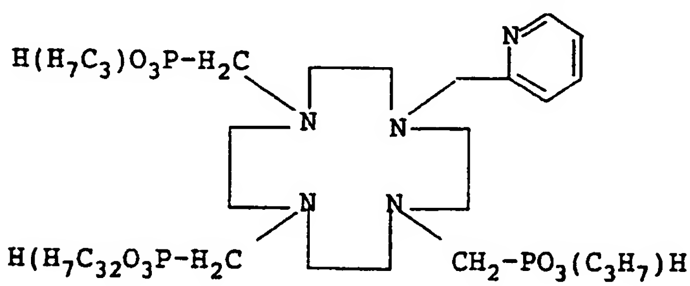
δ 1.24 - 1.36 (m, 9H), 1.95 - 2.04 (m, 6H), 3.03 - 3.29 (m, 22H), 4.10 - 4.25 (m, 8H), 7.74 - 7.92 (m, 2H), 8.23 - 8.29 (m, 1H), 8.87 - 8.96 (m, 1H); and

$^{13}C\{^1H\}$ NMR (D_2O, 353° K)

δ 13.15, 27.20, 50.43, 53.89, 54.48, 54.98, 55.42, 64.33, 69.41, 126.38, 128.30, 141.24, 152.46, 161.45; and

$^{31}P\{^1H\}$ NMR (D_2O, 353°K)

δ 21.61 (2P), 21.95 (1P); and is illustrated by the formula



The process to make the phosphonic acid derivatives of Formula (I) has been discussed before. A typical procedure is as follows:

Example 17: Preparation of N,N'-bis(methylenephosphonic acid)-2,11-diaza[3.3](2,6)pydinophane (BP2P).

A conc. HCl solution (37%, 4 mL) of N,N'-bis(methylenedimethylphosphonate)-2,11-diaza[3.3](2,6)pydinophane, prepared in Example 3, (255 mg, 0.53 mmol) was heated at reflux for 2.5 hr. After cooling, the solution was evaporated to dryness, followed by co-evaporation with fresh deionized water (3 X 2 mL) to eliminate excess HCl. The final product was isolated as a hygroscopic brown solid upon freeze-drying of the concentrated aqueous solution; and characterized by:

^1H NMR (D_2O)

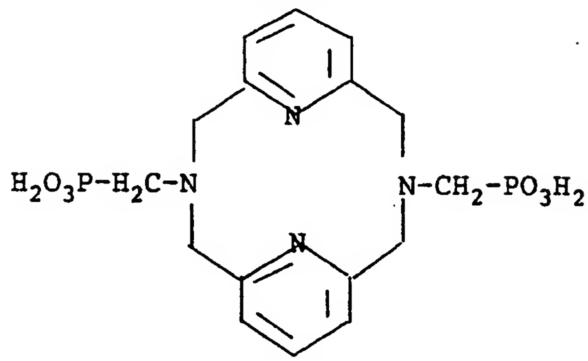
δ 3.55 (d, 4H), 4.46 (br s, 8H), 6.90 (d, 4H), 7.37 (t, 2H); and

$^{13}C\{^1H\}$ NMR (D_2O)

δ 57.80 (d), 63.74 (d), 127.02, 144.18, 152.96; and

$^{31}P\{^1H\}$ NMR (D_2O)

δ 11.71; and is illustrated by the formula



Example 18: Preparation of Ethylenediaminetetramethylenephosphonic acid (EDTMP).

To a cooled (0°C) THF solution (20 mL) of triethyl phosphite (23 g, 140 mmol) and paraformaldehyde (4.2 g, 140 mmol) was added ethylenediamine (2 g, 33.3 mmol) with stirring. After complete addition the solution was gradually warmed to room temperature and stirring continued for 12 hrs. The solution was then concentrated *in vacuo* to give the tetraethyl phosphonate ester as a viscous oil.

The tetraethyl phosphonate ester (2 g) was heated to 100°C for 6 hrs. in 12M HCl (50 mL). The solution was then cooled in an ice bath to give EDTMP as a white crystalline solid.

Other embodiments of the invention will be apparent to those skilled in the art from a consideration of this specification or practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with the true scope and spirit of the invention being indicated by the following claims.

CLAIMS:

1. A process for preparing azamacrocyclic or acyclic aminophosphonate ester derivatives which possess at least one secondary or primary nitrogen atom substituted with at least one moiety of the formula

$$-CH_2PO_3RR^1 \text{ (I)}$$

wherein:

R is H or C_1-C_5 alkyl; with the proviso that each R is the same group;

R^1 is C_1-C_5 alkyl, H, Na or K; with the proviso that each R and R^1 is the same group when C_1-C_5 alkyl;

which comprises reacting the corresponding unsubstituted amine compound with a trialkyl phosphite and paraformaldehyde to provide the derivatives of Formula (I) wherein all R and R^1 equal C_1-C_5 alkyl; and

(a) optionally followed by aqueous base hydrolysis to provide the derivatives of Formula (I) wherein R is C_1-C_5 alkyl and R^1 is H, Na or K; and/or

(b) optionally followed by acid hydrolysis to provide the derivatives of Formula (I) wherein all R and R^1 equal H.

2. The process of Claim 1 wherein the derivative product of Formula (I) has all R and R^1 equal C_1-C_5 alkyl.

3. The process of Claim 2 for preparing 1,4,7,10-tetraazacyclododecane-1,4,7,10-methylenedibutyl phosphonate which comprises reacting cyclen with tributyl phosphite and paraformaldehyde in THF.

4. The process of Claim 2 for preparing 1,4,7,10-tetraazacyclododecane-1,4,7,10-methylenediethyl phosphonate which comprises reacting cyclen with triethyl phosphite and paraformaldehyde in THF.

5. The process of Claim 2 for preparing N,N'-bis(methylenedimethyl-phosphonate)-2,11-diaza[3.3](2,6)pydinophane which comprises reacting 2,11-diaza[3.3](2,6)pydinophane with trimethyl phosphite and paraformaldehyde in THF.

6. The process of Claim 2 for preparing N,N'-bis(methylenediethylphosphonate)-2,11-diaza[3.3](2,6)pydinophane which comprises reacting 2,11-diaza[3.3](2,6)pydinophane with triethyl phosphite and paraformaldehyde in THF.

7. The process of Claim 2 for preparing N-(2-pyridylmethyl)-N',N'',N'''-tris-(methylenediethylphosphonate)-1,4,7,10-tetraazacyclododecane which comprises reacting N-(2-pyridylmethyl)-1,4,7,10-tetraazacyclododecane with triethyl phosphite and paraformaldehyde in THF.

8. The process of Claim 2 for preparing N-(2-pyridylmethyl)-N',N'',N'''-tris-(methylenedipropylphosphonate)-1,4,7,10-tetraazacyclododecane which compris s reacting N-(2-pyridylmethyl)-1,4,7,10-tetraazacyclododecane with tripropyl phosphite and paraformaldehyde in THF.

9. Th process of Claim 2 for preparing 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-methylenediethylphosphonate which comprises reacting 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene with triethyl phosphite and paraformaldehyde in THF.

10. The process of Claim 2 for preparing 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-methylenedi(n-propyl)phosphonate which comprises reacting 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene with tripropyl phosphite and paraformaldehyde in THF.

11. The process of Claim 2 for preparing 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-methylenedi(n-butyl)phosphonate which comprises reacting 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene with tributyl phosphite and paraformaldehyde in THF.

12. The process of Claim 1 wherein the derivative product of Formula (I) has all R equal H, Na or K and all R[1] equal C_1-C_5 alkyl.

13. The process of Claim 12 for preparing 1,4,7,10-tetracyclododecane-1,4,7,10-tetramethylenebutylphosphonate, tetrapotassium salt, which comprises reacting cyclen with tributyl phosphite and paraformaldehyde in THF to form 1,4,7,10-tetraazacyclododecane-1,4,7,10-methylenedibutyl phosphonate, followed by separating the formed intermediate, and then basic hydrolysis with KOH in a cosolvent of water and dioxane to form the desired product.

14. The process of Claim 12 for preparing N,N'-bis(methylenephosphonic acid ethyl ester)-2,11-diaza[3.3](2,6)pydinophane which comprises reacting 2,11-diaza[3.3](2,6)pydinophane with triethyl phosphite and paraformaldehyde in THF to form N,N'-bis(methylenediethylphosphonate)-2,11-diaza[3.3](2,6)pydinophane, followed by separating the formed intermediate, and then basic hydrolysis with KOH in water to form the desired product.

15. The process of Claim 12 for preparing 3,6,9,15-tetraaza-bicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-methylene(n-butyl)phosphonate tris(potassium salt) which comprises reacting 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene with tributyl phosphite and paraformaldehyde in THF to form 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-methylenedi(n-butyl)phosphonate, followed by separating the formed intermediate, and then basic hydrolysis with KOH in a cosolvent of water and dioxane to form the desired product.

16. The process of Claim 12 for preparing 3,6,9,15-tetraaza-bicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-methylene(n-propyl)phosphonate tris(potassium salt) which comprises r acting 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene with tripropyl phosphite and paraformaldehyde in THF to form 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-methylenedi(n-propyl)phosphonate,

followed by separating the formed intermediat , and then basic hydrolysis with KOH in water to form the desired product.

17. The process of Claim 12 for preparing 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-methyleneethylphosphonate tris(potassium salt) which comprises reacting 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene with triethyl phosphite and paraformaldehyde in THF to form 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-methylenediethylphosphonate, followed by separating the formed intermediate, and then basic hydrolysis with KOH in water to form the desired product.

18. The process of Claim 12 for preparing N-(2-pyridylmethyl)-N',N'',N'''-tris(methylenephosphonic acid ethyl ester)-1,4,7,10-tetraazacyclododecane which comprises reacting N-(2-pyridylmethyl)-1,4,7,10-tetraazacyclododecane with triethyl phosphite and paraformaldehyde in THF to form N-(2-pyridylmethyl)-N',N'',N'''-tris(methylenediethylphosphonate)-1,4,7,10-tetraazacyclododecane, followed by separating the formed intermediate, and then basic hydrolysis with KOH in water to form the desired product.

19. The process of Claim 12 for preparing N-(2-pyridylmethyl)-N',N'',N'''-tris(methylenephosphonic acid propyl ester)-1,4,7,10-tetraazacyclododecane which comprises reacting N-(2-pyridylmethyl)-1,4,7,10-tetraazacyclododecane with tripropyl phosphite and paraformaldehyde in THF to form N-(2-pyridylmethyl)-N',N'',N'''-tris(methylenedipropylphosphonate)-1,4,7,10-tetraazacyclododecane, followed by separating the formed intermediate, and then basic hydrolysis with KOH in water to form the desired product.

20. The process of Claim 1 wherein the derivative product of Formula (I) has all R and R^1 equal H, Na or K.

21. The process of Claim 20 for preparing N,N'-bis(methylenephosphonic acid)-2,11-diaza[3.3](2,6)pydinophane which comprises reacting 2,11-diaza[3.3](2,6)pydinophane with trimethyl phosphite and paraformaldehyde in THF to form N,N'-bis(methylenedimethylphosphonate)-2,11-diaza[3.3](2,6)pydinophane, which intermediate was acid hydrolyzed with heated HCl, and then the desired product separated.

22. The process of Claim 1 wherein the trialkyl phosphite is a tri(C_1-C_4 alkyl) phosphite.

23. The process of Claim 1, part (a), wherein the aqueous base is an alkali metal hydroxide.

24. The process of Claim 1, part (a), wherein the R or R^1 group is C_3-C_5 alkyl and an organic water miscible cosolvent is present.

25. The process of Claim 1 wherein the derivative of Formula (I) is an azamacrocyclic ligand where R and R^1 are both the same C_1-C_5 alkyl, and the temperature is maintained below 40°C during the first hour of the reaction.

26. The process of Claim 1 wherein the derivative of F rmula (I) is an azamacrocyclic ligand where R and R^1 are both the same C_1-C_5 alkyl, and a non-aqueous liquid is present.

27. The process of Claim 26 wherein the liquid is an aprotic polar solvent or alcohol.

28. The process of Claim 27 wherein the solvent is tetrahydrofuran.

29. The process of Claim 1 wherein the derivative of Formula (I) is an acyclic amine where R and R^1 are both the same C_1-C_5 alkyl, and the temperature is maintained below 40°C during the first hour of the reaction.

30. The process of Claim 29 wherein a trialkyl phosphite and paraformaldehyde are combined and initially cooled, followed by the controlled addition of the acyclic amine. and the temperature is maintained by using an ice bath.

31. The process of Claim 29 wherein the acyclic amine is ethylenediamine, diethylenetriamine, or triethylenetetraamine.

32. The process of Claim 31 wherein base hydrolysis provides the mono-alkyl phosphonates.

33. The process of Claim 32 wherein acid hydrolysis provides the corresponding phosphonic acids derivatives which are ethylenediaminetetramethylenephosphonic acid, diethylenetriaminepentamethylenephosphonic acid, or triethylenetetraamine-hexamethylenephosphonic acid.

34. The process of Claim 1 wherein the azamacrocyclic or acyclic aminophosphonate derivatives are represented by the formula

$$A\text{-}(N\text{-}CH_2CH_2\text{-}N)q\text{-}Z \quad (II)$$

wherein:

q is an integer from 1 to 5 inclusive;

A may be 0, 1 or 2 moieties of Formula (I) as claimed in Claim 1 or hydrogen;

Z may be 0, 1 or 2 moieties of Formula (I) as claimed in Claim 1 or hydrogen;

with the proviso that at least one A or Z moiety of Formula (I) as claimed in Claim 1 is present; and

A and Z may be joined to form a cyclic compound.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 94/05134

A. CLASSIFICATION OF SUBJECT MATTER

C 07 F 9/65

According to International Patent Classification (IPC) or to both national classification and IPC 5

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C 07 F 9/00,A 61 K,A 61 B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP, A1, 0 382 582 (CELLTECH) 16 August 1990 (16.08.90), abstract; page 8, line 37 - page 9, line 15. --	1-4, 12,13, 20
A	WO, A1, 90/01 034 (INTEROX CHEMICALS) 08 February 1990 (08.02.90), abstract; page 2, lines 10-24. --	1
A	WO, A1, 91/07 911 (CONCAT) 13 June 1991 (13.06.91), abstract; page 8, line 35 - page 9, line 10 (cited in the application). ----	1

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
02 August 1994	14. 09. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl. Fax (+ 31-70) 340-3016	REIF e.h.

ANHANG	ANNEX	ANNEXE
zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.	to the International Search Report to the International Patent Application No.	au rapport de recherche international relatif à la demande de brevet international n°

PCT/US 94/05134 SAE 91089

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The Office is in no way liable for these particulars which are given merely for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les reseignements fournis sont donnés à titre indicatif et n'engagent pas la responsibilité de l'Office.

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
EP A1 382582	16-08-90	AU A1 50436/90	05-09-90
		AU B2 633877	11-02-93
		CA AA 2026322	11-08-90
		GB A0 8903023	30-03-89
		JP T2 3504608	09-10-91
		WO A1 9009388	23-08-90
WO A1 9001034	08-02-90	EP A1 425577	08-05-91
		GB A0 8817185	24-08-88
WO A1 9107911	13-06-91	AU A1 67322/90	26-06-91
		AU B2 649001	12-05-94
		EP A1 513000	19-11-92
		JP T2 5504127	01-07-93
		US A 5236695	17-08-93